UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,628	01/26/2004	Veronique Trochon	1002-04	9953

35811 7590 04/15/2009

IP GROUP OF DLA PIPER US LLP
ONE LIBERTY PLACE
1650 MARKET ST, SUITE 4900
PHILADELPHIA, PA 19103

EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,628	TROCHON ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,16,17,20,21 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,16,17,20,21 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/26/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/17/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 13, 16, 17, 20, 21 and 23 are pending in this application. This office action is in response to an amendment filed 3/26/08.

Claim Objections

Claims 13, 17 and 21 are objected to because of the following informalities: the claims recite "A method of decreasing intratumoral vessels". However, the claim does not indicate what parameter about the vessels is decreased. As the specification sets forth that the method is directed to decreasing the number of vessels, it would be remedial to amend the claims to recite, for example, --decreasing the number of intratumoral vessels-- or --inhibiting formation of intratumoral vessels--.

As well Claims 13, 17 and 21 recite in the preamble specific desired outcomes. However, the following method only requires administration of an expression vector comprising SEQ ID NO:1 operably linked to an expression control sequence.

Appropriate correction is required.

Claims 17 and 21 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 13. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Based upon the amendment, the claims are singly limited to electrotransfer intramuscularly or intratumorally of a vector comprising SEQ ID NO:1 operably linked to an

expression control sequence. The consequence of this single step is inherently the same, decreasing number of vessels and thus inhibiting melanoma and pulmonary metastasis. As there is no distinction in the steps i.e. that the mammal only has melanoma or only has pulmonary metastasis and no way to separate treating pulmonary metastases, decreasing number of vessels or inhibiting growth of melanoma, the single step of electrotransfer of the vector would result in all three without distinction.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 16, 17, 20, 21 and 23 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of direct administration by electrotransfer to a melanoma or a pulmonary metastasis of a nucleic acid consisting of SEQ ID NO: 1 operably linked to an expression control sequence, wherein expression of SEQ ID NO:1 results in the decrease in the number of intratumoral vessels and in inhibition of growth of the melanoma or inhibition of the pulmonary metastases, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is maintained for reasons set forth**

7/9/08 and restated below. The rejection has been slightly reworded based upon applicants' amendment.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a methods of decreasing intratumoral vessels to inhibit growth of melanoma and pulmonary metastases, treating melanoma by decreasing intratumoral vessels to inhibit growth of the melanoma and a method of treating pulmonary metastases by inhibiting the metastases by decreasing intratumoral vessels by administration of a nucleic acid consisting of the polynucleotide sequence of SEQ ID NO:1 operably linked to an expression control sequence. The specification teaches that the disintegrin domain of metargidin when delivered to a tumor or metastases site can cause a diminution of vessels and thus lead to a decrease in pulmonary metastases and melanoma growth. The method recites quite broadly that the nucleic acid is delivered by electrotransfer to an intramuscular site or an intratumoral site. However, in order for diminution to occur, the sequence must be administered directly to the target site as set forth below. In the claims it is not clear what relationship the intratumoral site or intramuscular site have to the pulmonary metastases or melanoma targeted.

The adamalysin family functions in proteolysis, adhesion, fusion and intracellular signaling (see Ruben et al, US 2002/0182702 ¶ 1042). The art teaches that there are two subfamilies of adamalysins 1) snake venom metalloproteases (SVMPs) and 2) the ADAMS (proteins with a disintegrin domain and a metalloprotease domain). Multiple ADAMS have been identified including ADAM1, ADAMTS-1, fertilin (ADAM2), cryitestin (ADAM3), epididymal apical protein I, meltrin, MS2, TNF-a converting enzyme, Kusbanian and metargidin (see Ruben et al, ¶ 0004). Within the ADAMS, the disintegrin domain functions to prevent integrin-mediated cell to cell and cell to matrix interactions such as plated aggregration, adhesion, migration of tumor cells or neutrophils or angiogenesis. There have been multiple propositions that members of the adamalysin family have a potential to treat a myriad of conditions such as those recited here (see Ruben et al US 2002/0165377 and Young et al (US 2003/0194797 in which the role of ADAM-22 and any other ADAM protein in inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis is proposed), but these propositions have not lead to the identification of any treatments that are viable options against diseases. The specification states that metargidin comprises AMEP (anti-angiogenic metargidin peptide) and is a human protein with multipotent function including blocking angiogenic functions of integrin alpha v beta, inhibition of migration and formation of capillary structures and functions proapototically independent of modification of their cell cycle. The disintegrin domain constitutes Met 420 to Gly 511 of the full-length metargidin. However, SEQ ID NO:1 does not encode all of the metargidin domain. Rather, SEQ ID NO:1 encodes **the** disintegrin domain of metargidin and this disintegrin domain is encoded by all of SEQ ID NO:1.

The method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. In fact, the specification teaches, "Likewise, most transgenic protein expression is mostly, though not exclusively, restricted to the injection site. Such experiments have failed to demonstrate widespread expression of transgenic proteins in the brain beyond two months". As well, Verma et al (Verma and Somia, Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery.., the problem has been an inability to deliver genes efficiently and to obtain sustained expression". To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. In more advanced studies related to cancer, the art teaches "to bring about a desired therapeutic outcome. Reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle position in a tumour deposit." (Russell page 1165, col 2,¶ 4-5). In this case, the claims simply require administration intramuscularly or intratumorally. However, the relationship of the tumor targeted or the muscle targeted to the desired target is unclear. It is unclear if the tumor injected is the melanoma or other tumor related to the metastasis or if the muscle targeted is also related to either of these sites.

The specification is directed specifically to the analysis of AMEP, the disintegrin domain of metargidin encoded by Met 1 to Gly 91 of metargidin SEQ ID NO:1. Pages 8-9 describe specifically. Applicants synthesize AMEP in bacteria and demonstrate that this protein can function to inhibit adhesion of fibrinogen to vitronectin and fibronectin, inhibit endothelial cell migration, proliferation, capillary formation and stimulates proapoptosis in endothelial cells *in*

vitro. *In vivo,* AMEP nucleic acid was electrotransferred to muscle of nude and C57B1/6 mice and inhibited growth of MDA-MB-231 tumor growth and formation of pulmonary metastases in syngeneic mice. Applicants have amended the claims wherein the method requires electrotransfer intramuscularly or intratumorally presumably based upon these results. However, as set froth above, for human use generic methods of administration have not been successful. Furthermore, However, historically in vitro and animal models have not correlated well with in vivo clinical trial results in patients. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograph and nude mice experimental models and the human disease state. "Although animal studies have suggested low toxicity and excellent efficacy, these investigation have been limited by the use of immuno-deficient mice" (Meng and Diery p. 6, column 1). The success of any in vitro assays or in vivo animal models cannot be considered as evidence of success of treatment, in vivo results rarely correlate well with in vivo clinical trial results in patients and have not translated into successful human therapies. Many in vitro and animal models that are provided as evidence of success of treatment have not translated into successful treatments in humans. Ultimately the mouse model predicts agents that are effective in treating mice but not humans (see Gura, e.g. page 1041, col 1 and col 2, last paragraph). Therefore, the ability to predict potential success in humans based upon experimental results is highly unpredictable as demonstrated by the art. Rather for humans direct administration appears necessary to reduce non-desirable effects as well as to ensure full effect of delivered biomolecules.

The invention recites use of a broad group of means to decrease intratumoral vessels

which only requires that SEQ ID NO:1 be administered. Given the unpredictability of the art with regard to nucleic acid expression absent the construct to do so and the poorly developed state of the art with regard to nucleic acid stability once administered, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Response to Amendments

Applicants response filed on 1/8/09 have been considered but are not persuasive. Applicants have amended the claims to indicate that the nucleic acid is administered by electrotransfer intramuscularly or intratumorally. The instant method requires treatment of pulmonary metastasis and/or melanoma. Following administration there is no connection between the administration and the treatment. First, and as set forth above, it is not clear what relationship exists between the target site and the muscle or tumor receiving the nucleic acid. This is exacerbated by the unpredictable nature of gene therapy to avoid ancillary effects that are not desired as well as loss of function due to dissemination of the nucleic acid from the target site.

The Declaration under 37 CFR 1.132 filed 1/8/09 is insufficient to overcome the rejection of claims 13, 16, 17, 20, 21 and 23 based upon 112, first paragraph as set forth in the last Office action because: the results are not commensurate in scope with the claims. For reasons set froth above, the results *in vitro* and *in vivo* do not completely recapitulate the needs of human treatment. While human trials are not required, means of enabled treatment are required. The art

provided has allowed the case to be set forth that generic intramuscular and intratumoral administration will not provide the necessary effects. .

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13, 16, 17, 20, 21 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bettan et al (Bioelectrochemistry, 2000, pages 83-90; see entire document) in view of Fanslow et al (US 7074408; see entire document) and as evidenced by or further in view of Merkulov et al (US 6,294,368; see entire document). **This is a new rejection necessitated by applicants' amendment.**

Applicants claim a method of decreasing intratumoral vessels to inhibit growth of melanoma and pulmonary metastases in a mammal by administering SEQ IDNO:1.

Bettan et al teach methods of treating tumors and angiogenesis (production of tumoral vessels) by electrotransfer intratumorally. Bettan et al speak to the success of intramuscular administration in animals. Bettan et al do not speak to the nature of the gene to be introduced.

Fanslow et al teaches that disintegrin domains from a variety of ADAM proteins such as metargidin can be used to inhibit angiogenesis and endothelial cell migration (see e.g. abstract

and table 1). Fanslow et al do not provide the sequences used but as evidenced by Merkulov et al, the sequence is the same as SEQ ID NO:1.

As well, Merkulov et al isolate a protein comprising SEQ IDNO:11 (alignment below) and teaches that it is highly related to the ADAM disintegrins (see e.g. col 7, line 10-26). Merkulov propose administration of this molecule for treatment modalities (see e.g. bridging ¶ col 15-16).

```
Query Match             100.0%;  Score 549;  DB 4;  Length 814;
  Best Local Similarity   100.0%;  Pred. No. 4.1e-34;
  Matches   91;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 MAAFCGNMFVEPGEQCDCGFLDDCVDPCCDSLTCQLRPGAQCASDGPCCQNCQLRPSGWQ 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        420 MAAFCGNMFVEPGEQCDCGFLDDCVDPCCDSLTCQLRPGAQCASDGPCCQNCQLRPSGWQ
479

Qy         61 CRPTRGDCDLPEFCPGDSSQCPPDVSLGDGE 91
              |||||||||||||||||||||||||||||||
Db        480 CRPTRGDCDLPEFCPGDSSQCPPDVSLGDGE 510
```

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the disintegrin domain comprising protein taught by Merkulov et al or the disintegrin domain as taught by Fanslow et al in the methods taught by Bettan et al because Merkulov et al and Fanslow et al teach that it is within the ordinary skill of the art to use proteins comprising or disintegrin domains of metargidin in treatment of cancer and vessel formation and because Bettan et al teach that it is within the ordinary skill of the art to target treatments by electrotransfer into the tumor. As an initial point, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith* --USPD2d--., slip op. at 20, (BD. Pat. App. & Interfer.

June 25, 2007). In this case, it is obvious to combine known technologies with known products for predictable results and Bettan et al teach that it is known to administer treatment modalities on expression vectors encoding the product by electrotransfer and Merkulov and Fanslow et al teach that disintegrin domains provide successful therapeutic modalities. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Amendments

Applicants response filed on 1/8/09 have been considered but are not persuasive. Applicants argue that the invention is now limited to the disintegrin domain alone. However, the claim does not limit the biomolecule to that encoding only disintegrin. Rather the nucleic acid encoding disintegrin must consist of the sequences of SEQ ID NO:1. The vector however, is not limited to only those sequences. Rather, the vector can comprise any number of other sequences. Hence, the entirety of the protein of Merkulov et al encompasses the instant claims. Regardless of whether the recited function of Merkulov et al is due to the protease function or the disintegrin function, the protein is introduced to provide functions that encompass the instant functions. However, as set forth by Fanslow et al, the disintegrin domain alone can be used to provide functions such as inhibition of endothelial cell migration and angiogogenesis.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Primary Examiner
Art Unit 1633

/Maria B Marvich/
Primary Examiner, Art Unit 1633